THE SEVENTH ANNUAL REPORT
OF THE FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)
COLLABORATIVE RESEARCH PROJECT
JANUARY, 1998

Frederick S. Kaplan, M.D.
Eileen M. Shore, Ph.D.

Several important discoveries occurred in FOP research during 1997. In addition, an intensive international collaborative research effort to determine the chromosomal location and identity of the FOP gene using genetic linkage analysis was initiated. This new project was made possible by the addition of DNA samples from a newly discovered multi-generational FOP family from France and from a multi-generational family from Louisiana. These additional samples now enable us to use powerful linkage analysis in an attempt to identify the genetic location of the FOP gene. As recently as six months ago, we said "the usual approach to identifying the genetic basis of a disease, genetic linkage analysis and positional cloning, presently is impossible for FOP due to the small number of affected individuals and the lack of multi-generational families showing inheritance of the disease." The addition of DNA samples from the French and Louisiana families more than doubles the number of informative individuals in our genetic data bank and enables us to use powerful molecular techniques to search for the chromosomal location of the damaged gene. Although we are still short of the critical number of DNA samples (from multi-generational families) necessary to identify the damaged FOP gene, we have made a giant step forward.

Laboratory studies performed by the FOP collaborative research group in 1997 were extensive and focused on four major approaches to investigate FOP: 1. The genetic approach: to identify the disease-causing gene that is altered in FOP. 2. The molecular approach: to examine differences in gene expression in FOP including bone morphogenetic protein 4 (BMP-4) -- which we have found to be over-expressed in FOP -- and other candidate genes, to understand the effects of these gene expression differences in FOP, and to understand molecular pathways involved in heterotopic ossification. 3. The physiologic approach: to investigate the cellular differentiation and developmental events that lead to osteogenesis at heterotopic sites. 4. The therapeutic approach: to use the knowledge discovered in the laboratory to design therapies that will be genuinely useful to people who have FOP.

THE GENETIC APPROACH

The goal of the genetic approach is to identify the disease-causing gene in persons who have FOP. Two strategies can be used to identify the gene responsible for a genetic disease. In the first strategy, specific genes that could be involved in FOP based on their known functions are examined. This candidate gene (or educated guess) approach examines plausible genes one by one. The alternate strategy is a genome-wide search for the disease-causing gene. This approach does not hypothesize which gene is involved, but instead is open to the possibility that any of the genes located on the chromosomes could be the disease-causing gene. A genome-wide search strategy has the greater chance of successfully identifying the gene responsible for a genetic disease, however this analysis generally requires the availability of several multi-generational families showing inheritance of the disorder.

In a genome-wide search, the gene responsible for a genetic disease can be identified by finding a known molecular (DNA) marker on the chromosomes that is co-inherited with the (unknown) gene that causes the disorder. Such a marker will be located very near the gene of interest, and will provide an important positional signal or "link" to allow the identification of the specific gene through a procedure known as positional cloning. Such a localization procedure, known as linkage analysis, could not be effectively used to search for the damaged gene for FOP until very recently, since many families with multiple affected members are needed to perform such an analysis, and such families had not yet been identified in the FOP community. However, during this past year, physicians and scientists from the Association Francaise Contre Les Myopathies identified a multi-generational family from France. In addition, DNA samples from a multi-generational family from Louisiana have become available. The addition of the DNA samples from these two families to the international effort has dramatically enhanced the power of our investigation to identify
the damaged gene in FOP. Even six months ago, such an approach was but a distant dream. Much of course, depends on whether FOP is caused by the same damaged gene in each family or by a different damaged gene in each family. While some evidence suggests that different genes may be involved in different families, other evidence points to the hypothesis that one gene may be the cause of the disorder is all affected families. Currently four families with autosomal dominant inheritance of FOP have been identified worldwide [United States(2), United Kingdom(1), and France(1)]. Intensive efforts began in the laboratory in late 1997 to perform the genome-wide linkage analysis.

In addition to our genome-wide linkage analysis of FOP, we continue to pursue a candidate gene

strategy as well. This is essentially an educated guess approach as to which genes may be involved based upon the clinical findings and natural history of the disease. Many of our discoveries involving BMP-4, including the important finding that BMP-4 is over-expressed in cells from many patients with FOP, have revolved around the candidate gene approach. While we know that BMP-4 is involved in the pathology and pathophysiology of FOP, subsequent studies have not identified mutations in the protein-codeing region of the gene.

A genetic analysis using DNA markers near the BMP-4 gene would allow us to test if the BMP-4 gene is linked to FOP, perhaps due to a mutation in a regulatory region of the gene (as opposed to the protein coding region of the gene). DNA markers near the BMP-4 gene could be used in linkage exclusion analysis to see if they follow the same inheritance pattern as FOP in the few affected families that have been identified. If markers that are very close to the BMP-4 gene follow the exact inheritance pattern as FOP in affected family members, that would provide support for BMP-4 as the causative gene for the disorder. However, if linkage markers very close to the BMP-4 gene do not follow the same inheritance pattern as FOP in affected family members, then the BMP-4 gene would be excluded from further consideration as the primary causative gene in FOP. Since markers for the BMP-4 gene had not been identified, it was necessary for us to search for such markers in order to accomplish this study. In 1996, we discovered a useful DNA marker very near the BMP-4 gene (as well as one actually within the BMP-2 gene) that could be used in such an analysis. In late 1997 we used those markers in our FOP family studies and were able to exclude the BMP-2 gene as a source of the genetic mutation in all four FOP families. In addition, we were able to exclude BMP-4 as the source of the genetic mutation in two of the FOP families, however in another small FOP family, whose affected members exhibit dramatic over-expression of BMP-4, linkage to the BMP4 gene remains possible.

Thus, while the disease-causing gene for FOP resides at some still unidentified locus in the human genome, BMP-4 is inevitably involved in the signaling pathways that govern formation of an ectopic chondro-osseous lesion. Sites of genetic damage could reside in the promoter (switch) of the BMP-4 gene, in other genes whose protein products act on the promoter of the BMP-4 gene, in downstream portions of the BMP-4 signaling cascade whose feedback control is linked to BMP-4 activity, or in other molecular and signaling pathways that intersect the BMP-4 pathway. In other words, the genetic mutation or mutations that cause FOP could plausibly reside anywhere in the BMP-4 signaling pathway or in other signaling pathways that have effects on the level of BMP-4 expression. Numerous plausible upstream candidate loci have been identified and are currently being examined. In the broader sense, the research involves an analysis of the genetic and molecular pathways that are ectopically and inappropriately activated in patients who have FOP. Our search for plausible candidate genes for FOP has expanded dramatically in the past year.

Although localization and identification of the diseased gene is necessary for understanding FOP, it is only a first step in the process of developing successful therapeutic treatments. As George Scangos wrote in Drug Discovery in the Post-Genomic Era (Nature Biotechnology, Volume 315, p. 1220-1221; November 1997), "To date, technologies have identified many genes whose differential expression correlates to disease. However, it has been difficult to determine which differentially expressed genes, if any, are cause rather than effect, and which, if targeted by a drug, could reverse a disease process. The positional cloning approach for discovering diseased genes has been extraordinarily successful from a scientific perspective by combining significant resources and strong science. Many groups -- from both Universities and Drug Discovery Companies -- have identified and cloned genes involved in human diseases. The problem is that while these genes provide insight into the causes of disease, they too are limited in what they can deliver for therapeutic intervention. Targeting the diseased gene itself may not be the answer. Using the gene to understand the biochemistry and regulation of the appropriate pathways and thereby identify an optimal point of intervention is the key. Biological processes normally exist in a state of homeostatic balance (equilibrium). Diseased states arise when the equilibrium is perturbed. Diseased genes almost certainly act by disturbing the equilibrium. Based on this understanding, ideal screening targets are those genes and proteins whose inhibition by a drug would counteract the effects of a diseased gene by restoring equilibrium. In other words, those drug developers who can answer the question what genes and proteins exist in the target cells, which when inhibited by a drug will reverse the effects of a diseased gene and restore equilibrium, will be the first to develop important new drugs. Most biological processes are under both positive and negative control, and are affected

by multiple biochemical pathways. It is therefore likely that
such genes and proteins exist for almost all diseased genes. To find these genes, one must characterize the biochemical pathways and networks in which the diseased gene operates, and one must identify and characterize other
biochemical pathways that affect the same biological process."

This multifaceted approach that Scangos describes has characterized our work on FOP during the past year and has enabled us to identify candidate genes and candidate gene pathways whose homeostatic balance (equilibrium)
is disturbed in FOP. Thus, the discovery in 1997 of upstream stimuli and downstream targets of BMP-4 action in normal and FOP cells enabled a much more comprehensive understanding of the cellular and molecular signaling pathways that may be activated during heterotopic ossification in patients who have FOP. Such information is critical in designing strategies that will enable effective inhibition of heterotopic ossification.

Identification of the disease-causing gene in FOP, whether by a candidate gene or a genome-wide analysis approach, will provide tremendous insight into the causes of this disease. However, the biochemical pathways and
networks in which the diseased gene operates as well as other biochemical pathways that affect the same biological process must be identified and characterized in order to develop the most effective treatments for FOP. This perspective leads us to our next approach, which we describe as the molecular approach.

THE MOLECULAR APPROACH

The focus of the molecular-approach is to understand the molecular pathways of ectopic bone formation in which BMP-4 acts; in other words, to understand the molecular switches that regulate BMP-4 activity as well as the molecular switches that BMP-4 regulates. Preliminary studies on the structure of the switch in the BMP-4 gene have been completed, and the final paper is in press in a major scientific journal. It is possible that the BMP-4 switch is damaged in people who have FOP. It is also possible that one of the proteins that turns the switch on and off (these proteins are made from separate genes in a different parts of the chromosomes) is abnormal. Understanding the on-off switching mechanism of the BMP-4 gene in muscle cells and bone cells will have great value in designing effective
treatments for FOP.

The discovery of the over-expression of BMP-4, a powerful bone inducing hormone, in the lymphocytes of approximately eighty percent of patients with FOP provided an important foundation for many of last year's exciting
research developments. In an unexpected discovery, we found that BMP-4 was expressed in bone marrow stem cells that give rise to all cells of the circulating blood and some cells of the immune system. We reported these findings in August, 1997 at a special invited lecture at the National Institutes of Health. We had demonstrated that extra copies of the human BMP-4 gene can be genetically engineered into blood borne cells of the immune system in transgenic animals in attempt to mimic the misexpression and/or overexpression of BMP-4 in patients with FOP. These findings have important implications for understanding the complex molecular and cellular events that occur during heterotopic bone formation in FOP, and for designing successful treatment strategies to deliver high concentrations of biologically active BMP-inhibitors to sites of tissue injury in patients who have FOP.

Important discoveries were made in 1997 on the receptors for the BMP proteins. These receptors exist on cell membranes. When BMP-4 binds to its protein receptors on the cell membrane, it causes the receptor to undergo a
molecular and structural change. This change in receptor conformation transmits a signal to the nucleus of the cell through a series of protein messengers that enable the cell to respond to the signal in an appropriate manner. Proteins called SMADs enter the nucleus of the cell, bind to the DNA of other genes, and turn those genes on or off.

Detailed knowledge of the receiving and transmitting requirements for BMP signaling have been identified in the past year, and we have begun to study those signaling pathways in FOP cells. It appears that FOP cells make the
identified signaling molecules, but we are not yet certain whether the signals are being transmitted in an appropriate manner inside the cell. Levels of BMP receptor messenger RNAs appear to be normal compared to individuals who do not have FOP. Yet, while these levels may appear to be appropriate at first glance, the regulation of these molecules inside the cell may be inappropriate for the level of the outside BMP-4 message. To add a further level of complexity to this picture, there are also antagonist pathways to BMP-4 signaling inside the cell that can inhibit or dampen the BMP-4 signal. It is plausible that damage

(mutation) to one of the genes controlling an inhibitory pathway could lead to elevation of the BMP-4 signal, and such possibilities are being vigorously investigated in the laboratory. Thus, while an enormous amount of new knowledge has been discovered about BMP-4 signaling over the past year, the complexities of the BMP-4 signaling pathway (under normal circumstances and in FOP) make this system extremely challenging to understand. It is very clear that the BMP-4 gene itself is but one of many genes involved in the BMP-4 signaling pathways.

Several of the genes involved in the BMP-4 signaling pathways have been recognized as tumor suppressor genes. These are genes that normally act to regulate cell division. Mutations in these genes may lead to uncontrolled
proliferation of cells. It is inevitable that these tumor suppressor genes are involved in the evolution and development of FOP lesions. While these genes may or may not harbor the mutation that causes FOP, they are certainly involved in the FOP process and are therefore potential targets for therapy. Study of tumor suppressor genes in the BMP-4 pathway is underway in the laboratory and will likely lead to important insights for FOP therapy.

During the past year, we discovered that exostoses (benign tumorous outgrowths from the skeleton) are a relatively common feature of FOP and that the genes involved in the formation of exostoses (EXT 1, 2, 3, and EXT-L) which are mutated in patients with multiple hereditary exostoses, are plausibly involved in BMP-4 signaling pathways. Since exostoses often arise from the skeleton of patients who have FOP, and the EXT genes are involved in the formation of exostoses, it is also possible that these genes play a role in FOP.

During the past year extensive experimental data confirmed the discovery that basic fibroblast growth factor (a signaling molecule involved in bone formation during embryogenesis, in fracture healing post-natally, and in
the recruitment of new blood vessels at sites of inflammation) is produced and excreted at elevated levels during FOP flare-ups (but not at times of disease quiescence). This discovery greatly expands our knowledge of the molecular pathways that are recruited during heterotopic ossification in FOP. Basic fibroblast growth factor (bFGF) is an extremely potent molecule involved in the growth and spread of tumors and is now firmly implicated in the pathophysiology of FOP. Basic fibroblast growth factor and BMP-4 are intimately involved in pathways of embryonic bone formation as well as in
postnatal bone formation and heterotopic ossification. The elevation of basic FGF during FOP flare-ups clearly marks this molecule as an important target for therapy to inhibit heterotopic bone formation.

A critically important question about FOP that must be addressed and answered is: Are FOP lesions monoclonal tumors or polyclonal reactive lesions? The evolution of pre-osseous FOP lesions into mature bone and the extremely rapid appearance of fibroproliferative lesions suggests that they may be polyclonal reactive lesions, much like a fracture. However, the spontaneous regression of some pre-osseous FOP lesions suggests the alternate hypothesis (that they may be tumors arising from a single abnormal clonal cell). Also, early pre-osseous fibroproliferative lesions
in FOP dramatically resemble those seen in a condition called aggressive juvenile fibromatosis (AJF). This latter lesion has been shown recently to be a monoclonal tumor rather than a polyclonal reactive lesion. The clear identification of FOP lesions as either monoclonal tumors or polyclonal reactive lesions will help greatly in understanding molecular pathways recruited during the development of lesions. Such studies are currently underway in our laboratory. They require the availability of abundant pre-osseous fibroproliferative tissue obtained during biopsy in children with FOP, as well as the use of molecular techniques to determine the differential silencing of genes on one or both copies of the X chromosome in lesional biopsy specimens (obtained from young females, all of whom have 2 copies of the X-chromosome). The results of these experiments should be forthcoming in the next year and will enhance our understanding of the molecular pathways and the pathophysiologic processes leading to FOP lesions. As with other approaches, such knowledge will help in designing effective therapies to inhibit the growth and spread of FOP lesions.

THE PHYSIOLOGY (ANIMAL MODEL) APPROACH

In addition to the genetic and molecular approaches, animal models of bone formation continue to play an extremely important role in understanding the process of bone formation in FOP. Each animal model provides a slightly
different perspective on bone formation and each one was carefully chosen or developed to examine one or more features of early bone formation pathways. Some of the most valuable models are those in which a gene in the
bone formation pathway has been genetically removed. One such model, developed by a collaborator at the University of California - Berkeley, involves the removal of an important inhibitory gene in the BMP signaling pathway. Animals lacking both copies of a gene called noggin form extra bone and die soon after

birth from malformation of the chest wall.
However, animals who lack one copy of the gene appear to be entirely normal. Experiments will soon begin to determine whether the clinically normal appearing animals (who lack one copy of the noggin gene that inhibits BMP4 activity) have an increased susceptibility to forming heterotopic bone.

In another animal model using recombinant human BMP-induced formation, we have identified molecular markers of angiogenesis (blood vessel formation) in the early pre-osseous lesions. Such molecular markers may be important
targets for anti-angiogenic therapy in FOP. The requirement for blood vessel development in bone formation has been well established, and we are studying its role in FOP.

In another very important model, we have developed animals transgenic for BMP-4 by over expressing the BMP-4 gene in circulating lymphocytes (a blood-borne immune cell that produces antibodies). We have shown that extra copies of the BMP-4 gene can be genetically engineered into these cells, and that the animals express BMP4 in the B lymphocytes (while normal wild type animals do not). While no heterotopic bone has formed in these animals, the early inflammatory response to injury closely resembles the perivascular inflammatory response seen in the earliest FOP lesions
Although both B and T lymphocytes have been identified in early FOP lesions, the T lymphocytes appear to invade the skeletal muscle and preside at sites of muscle damage. Consequently, we are currently making transgenic animals that overexpress BMP-4 in T lymphocytes. If lymphocytes mediate osteogenesis by overproducing and secreting BMP-4, then it is possible that B and T lymphocytes will both be necessary to see the effect. Work will continue in 1998 on these important transgenic experiments.

An FOP-like condition has been previously identified in the cat. Unfortunately no live cats with the FOP-like condition are available, so current studies are being performed on preserved tissues. Lymphocytes in the early lesions of the cat also show evidence of BMP4 overproduction. An article will soon be published on the histologic appearance of early pre-osseous fibroproliferative lesions in the cats. The lesions appear identical to those seen in children with FOP. This work is being pursued in collaboration with investigators at Cornell University.

Another useful animal model in our study of FOP involves the embryonic overexpression of the protein called Fos, the product of the Fos proto-oncogene, and a potent transcription factor that acts directly to turn-on and turn-off other genes. Fos is likely an important regulator of the BMP-4 gene, and an important signaling molecule in endochondral ossification. Work in our laboratory has identified the overexpression of Fos and BMP-4 in transgenic animals that have an FOP-like condition. The exact role that Fos plays in regulating the BMP-4 gene must be deciphered in order to understand the molecular and developmental pathways of bone formation in FOP. This work is being pursued in collaboration with investigators at The University of London in England, and The Institute for Molecular Pathology in Vienna, Austria.

Another animal model under development involves the implantation of bone marrow stem cells from patients who have FOP into mice that are genetically engineered to accept such a stem cell transplantation. This model will
test the hypothesis that bone marrow stem cells in patients who have FOP give rise to cells that circulate in the blood, escape into muscle, overproduce BMP-4, and lead to ectopic bone formation. While it is unfeasible to obtain bone marrow stem cells from FOP patients by direct needle aspiration, bone marrow stem cells will be coaxed out of the bone
marrow by the use of a drug called granulocyte colony stimulating factor (G-CSF) and collected from the peripheral blood of FOP patients. These cells will then be purified and injected into mice that are engineered to accept such stem grafts. The role that the BMP genes play in this process will be studied in this animal model and the mice will be observed over time to see if they develop an FOP-like condition. Preliminary studies conducted in 1997 showed that BMP-4 was expressed in hematopoietic (blood-making) stem cells from the bone marrow of normal and FOP patients, as well as in mature T-lymphocytes, and monocytes (but not in granulocytes or B-cells from normal controls).

Another important animal model involves the transplantation of genetically-marked hematopoietic and marrow stromal stem cells into a normal host animal that has received an intramuscular injection of recombinant human BMP-4. Such transgenic animal experiments will enable us to follow the maturation of genetically-marked stem cells through
developmental pathways involved in heterotopic bone formation. The origin and fate of bone-forming cells in heterotopic ossification is presently not understood.

In a related experiment, animals whose muscle satellite cells are genetically tagged by the expression of a specific muscle transcription factor will be used to identify the fate of these muscle satellite cells in heterotopic ossification. This work is critically important to FOP since it has long been thought that the

pre-osseous fibroproliferative cells in FOP lesions arise from the connective tissue of skeletal muscle. While these connective tissue cells are generally difficult to distinguish from primitive muscle cells, the tagged muscle cells can be followed throughoutheterotopic bone formation.

Recent experimental data suggests that one of the two forms of the Type I BMP receptor (BMP4R-1B) mediates cartilage cell proliferation and programmed cell death while the other form of the Type I BMP receptor (BMP4R-1A) mediates cartilage cell differentiation and BMP activity during later bone formation. Animal models that selectively inhibit one of the two forms of the Type I BMP-4 receptor activity have been very helpful in understanding embryonic pattern forming events and post-natal bone forming events mediated by BMP. Such animal models are useful to us in studying programmed cell death (apoptosis) that prevails in the fibroproliferative cells of early FOP lesions and that may play an important role in the spontaneous regression of fibroproliferative lesions. The preliminary findings suggest the possibility that regulation of the BMP receptors may determine whether a pre-osseous lesion undergoes spontaneous regression or whether it develops into mature heterotopic bone. Therefore, factors that regulate the expression not only of the BMP-4 gene, but of the two major isoforms of the type I BMP-4 receptor may be even more critical in understanding the spontaneous regression of some early fibroproliferative lesions. These new insights in understanding BMP gene expression, BMP receptor expression, and BMP signaling pathways have been gained from studying these animal models and have had immediate application to understanding FOP.

TREATMENTS FOR FOP

The ultimate goal of all FOP research is to cure FOP and we continuously strive to apply knowledge discovered in the laboratory to the development of novel therapies. During the past year, intensive collaborative work has continued with scientists from two pharmaceutical companies on developing novel medicines to treat FOP. Each potential therapy is a direct result of information from the molecular and cellular studies investigated in the FOP laboratory.

One potential drug called squalamine is a unique amino-sterol discovered in the dogfish shark and now derived synthetically. Squalamine potently inhibits the formation of new blood vessels. Since new blood vessels are required to form bone, it is possible that squalamine may inhibit bone formation. Early experiments with squalamine have shown a potent dose response effect on the inhibition of blood vessel formation. During 1997, intensive preclinical studies were performed to examine the effect of squalamine on the earliest events of blood vessel formation. The data suggest that squalamine may affect the activity of receptors on the surface of endothelial (blood vessel forming) cells. In late 1997, Phase I clinical trials were started to determine the safety and pharmacokinetics of intravenously administered squalamine in humans. The results of these studies, forthcoming during 1998, will be used to design the long-awaited
clinical trials of squalamine for the treatment of FOP.

Last year, our scientific collaborators at another pharmaceutical company reported that the protein noggin avidly binds to BMP-4 and antagonizes its activity. The underproduction of noggin leads to increased BMP-4 activity
and to ectopic bone formation in an animal model. These findings suggested the potential use of noggin in treating FOP. Collaborative studies were conducted to examine the effects of noggin on inhibiting BMP induced bone
formation in an animal model. These early pre-clinical studies have dramatically shown proof of the principle that noggin can effectively inhibit BMP-induced heterotopic bone formation. Currently, intensive collaborative work continues in developing noggin for the treatment of FOP.

MEETINGS, REPORTS, AND PUBLICATIONS

In February 1997, the European Neuromuscular Center (ENMC) sponsored an international workshop on FOP in Naarden, the Netherlands. This small meeting was attended by eleven members of the international FOP consortium from England, France, Germany, Italy, and the United States. Professor Roger Smith (Oxford) and Frederick Kaplan (University of Pennsylvania) were co-Chairmen of the workshop.

The workshop was extremely helpful in allowing a small and interested group of international collaborators to exchange information rapidly, and to engage in intense discussion on the molecular, cellular, and physiologic aspects of FOP. As a result of this small meeting, the international collaborative effort on FOP was expanded to include participating members
from the Association Francaise Contre Le Myopathies, as well as investigators from the Nuffield Orthopaedic Center in Oxford, England, and The MRC Bone Research Laboratory at Oxford University.

During 1997, international presentations of FOP research were made bymembers of the FOP Laboratory at:

The ENMC sponsored international workshop on FOP; Naarden, The Netherlands.
The IFOPA - Children's Symposium; Orlando, Florida.
The American Society for Bone and Mineral Research; Cincinnati, Ohio.
The National Institutes of Health; Bethesda, Maryland.

The Portland Bone Symposium; Portland, Oregon.
The University of California - San Francisco, San Francisco, California.

During the past year, twenty research articles on FOP were written, reviewed, and edited, and will be published in January 1998 in an issue dedicated to FOP in Clinical Orthopaedics and Related Research, a leading journal of musculoskeletal science. Articles will appear on the following topics:

1) Editorial comments on FOP research
2) Historical perspective on FOP
3) FOP: clinical lessons from a rare disease
4) The genetics of FOP
5) Acute lymphocytic infiltration in an extremely early lesion of FOP
6) Bone morphogenetic proteins
7) Characterization of BMP4 receptors in FOP
8) Differential expression of bone and cartilage related genes in FOP, myositis ossificans traumatica, and osteogenic sarcoma
9) Mutational screening of the bone morphogenetic protein 4 gene in a family with FOP
10) Urinary basic fibroblast growth factor: a biochemical marker for pre-osseous fibroproliferative lesions in patients who have FOP
11) The HLA-B27 Allele is not correlated with FOP
12) Animal models of heterotopic ossification
13) Embryonic over-expression of the c-Fos proto-oncogene: a murine stem cell chimera applicable to the study of fibrodysplasia ossificans progressivain humans
14) Similarities in the phenotypic expression of pericytes and bone cells
15) Pulmonary and cardiac function in advanced FOP
16) Catastrophic falls in patients who have FOP
17) Effects of intravenous Etidronate in acute episodes of FOP: an open study
18) Treatment of patients who have FOP with 13-cis-retinoic acid (Isotretinoin)
19) A growth related mechanism of superior subluxation of the glenohumeral joint in patients who have FOP
20) Pseudomalignant heterotopic ossification in childhood: comparisons and contrasts to FOP and soft tissue osteosarcoma

THE FOP LABORATORY

The current staff of the FOP Research Laboratory includes eleven individuals: 2 principals investigators, 3 research specialists, 2 postdoctoral fellows, one orthopaedic research fellow, one graduate student, and 2 medical students. The FOP Laboratory currently occupies nearly 1000 square feet of space. Plans are currently underway to expand research space in the FOP laboratories. The Department of Orthopaedic Surgery at the University of Pennsylvania has committed an additional 1000 square feet of space to FOP research. The space is currently being renovated and will be available for expanded research activities by mid-1998.

CAUSE AND CURE

Dramatic progress continues to be made in understanding the genetic, molecular, cellular, and physiologic basis of FOP. Cause and cure are the two words that continue to propel the International FOP Collaborative Research Effort and provide the guiding principle for all we do: to discover the exact molecular cause of FOP and to use that knowledge to develop therapies that will be truly effective in preventing, treating and curing FOP. 1997 was a year of tremendous growth in the FOP effort and was highlighted by the recruitment of the powerful genome-wide linkage analysis to the search for the mutated gene. We are hopeful that 1998 will be a year of great milestones in FOP research.

As always, "finding the cure for FOP is not a job, it is a mission." We are all extremely proud to be a part of that mission, and we are enormously grateful to those who support this vital research effort:

1) The International FOP Association
2) The National Institutes of Health (the people of the United States of America)
3) The Ian Cali Fund for FOP Research
4) The Isaac and Rose Nassau Professorship of Orthopaedic Molecular Medicine
5) The European Neuromuscular Center
6) The Medical Research Council (United Kingdom)
7) The Association Francaise Contre Les Myopathies (France)
8) The Gund Foundation
9) Members of the FOP Research Consortium
10) The many individuals, families and friends throughout the world who contribute to the FOP effort

We will continue to need your generous help until a cure is found. Thank you.